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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/826,466	04/16/2004	William H. Andrews	SIER-022CON	1298
24353	7590	01/03/2006	EXAMINER	
BOZICEVIC, FIELD & FRANCIS LLP 1900 UNIVERSITY AVENUE SUITE 200 EAST PALO ALTO, CA 94303			NOBLE, MARCIA STEPHENS	
			ART UNIT	PAPER NUMBER
			1632	

DATE MAILED: 01/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 10/826,466	<b>Applicant(s)</b> ANDREWS ET AL.	
	<b>Examiner</b> Marcia S. Noble	<b>Art Unit</b> 1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on 21 November 2005.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 46,48 and 49 is/are pending in the application.
- 4a) Of the above claim(s) 1-45,47 and 50-52 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☐ Claim(s) \_\_\_\_\_ is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                        | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)               | Paper No(s)/Mail Date. _____  |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date <u>3/08/2005</u> .   | 6) <input type="checkbox"/> Other: _____                                    |

### DETAILED ACTION

1. Applicant's election with traverse of group XIX, claims 46, 48, and 49 in the reply filed on 11/21/2005 is acknowledged. The traversal is on the ground(s) that it would not be unduly burdensome to perform a search on all of the claims together in the instant application. This is not found persuasive because the additional queries necessary to perform to encompass all the claims would be considered undue. To include a search of the claims in other groups, additional queries including nucleic acid treatment, protein treatment, small molecules and SEQ ID 1 what encode decoys that range between 10 to about 50 bases that enhance TERT expression would have to be added. The terms ex vivo and in vivo would be required in the searches. Another query would involve aspect of searching telomerase activity and another would require the addition of increase, inhibit, reduce, drug, pharmaceutical, therapy, therapeutic, as well as screen through the various drugs that would potentially have the various effects. Each additional query would have to be run and results assessed in multiple databases. This amount the additional search would require unique and separate searches and would be considered undue.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-45, 47, and 50-52 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected group, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 11/21/2005.

Claims 46, 48, and 49 are under consideration.

***Priority***

2. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. [1] as follows:

It is noted that this application appears to claim subject matter disclosed in prior Application No. 10/675,794, filed 09/29/2003. A reference to the prior application must be inserted as the first sentence(s) of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e), 120, 121, or 365(c). See 37 CFR 1.78(a). For benefit claims under 35 U.S.C. 120, 121, or 365(c), the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of all nonprovisional applications. If the application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference to the prior application must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted

during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A benefit claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed benefit claim under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

If the reference to the prior application was previously submitted within the time period set forth in 37 CFR 1.78(a), but not in the first sentence(s) of the specification or an application data sheet (ADS) as required by 37 CFR 1.78(a) (e.g., if the reference was submitted in an oath or declaration or the application transmittal letter), and the information concerning the benefit claim was recognized by the Office as shown by its inclusion on the first filing receipt, the petition under 37 CFR 1.78(a) and the surcharge

under 37 CFR 1.17(t) are not required. Applicant is still required to submit the reference in compliance with 37 CFR 1.78(a) by filing an amendment to the first sentence(s) of the specification or an ADS. See MPEP § 201.11.

### ***Specification***

3. The nucleotide sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825.

37 CFR 1.821(d) states: "[w]here the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description of claims, even if the sequence is also embedded in the text or the description or claims of the patent application.

Page 34, sec [96], par 2, last line: Sequence containing greater than 10 na require SEQ ID NO.

Appropriate correction is required.

The absence of proper sequence listing did not preclude the examination on the merits however, **for a complete response to this office action, applicant must submit the required material for sequence compliance.**

### ***Claim Objections***

4. Claim 46 objected to because of the following informalities:

"A method of determining whether an agent that inhibits GC-Box 5 repression of TERT transcription" suggests the "agent" has another primary function in the instant application other than inhibiting GC-Box 5 repression of TERT transcription.

Appropriate correction is required.

### ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 46, 48, and 49 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-4 and 6-16 of copending Application No. 11/198,933. Although the conflicting claims are not identical,

they are not patentably distinct from each other because the breath of the claims from both applications encompass the same embodiments.

The instant application is drawn to a method comprising: (a) contacting a small molecule with an expression system comprising a GC-Box 5 repressor binding site and a coding sequence operably linked to a TERT promoter, under conditions such that in absence of said small molecule, transcription of said coding sequence is repressed in a cell; (b) determining whether transcription of said coding sequence is repressed in the presence of said small molecule; and (c) identifying said small molecule as an agent that inhibits GC-Box repression of TERT transcription if transcription of said coding sequence is not repressed in the presence of said small molecule.

The copending application is drawn to a method comprising contacting an agent with an expression system comprising a TERT promoter nucleic acid sequence linked to a heterologous reporter nucleic acid, wherein said expression system is integrated into a nucleic acid in a manner such that it is known to be inactive under wild-type conditions but not positionally silenced and evaluating transcription of said heterologous reporter nucleic acid to determine whether said agent modulated transcription control activity of said TERT promoter nucleic acid.

The copending application broadly claims "an agent" which encompassed the more narrowly claimed "a small molecule of the instant application. The copending application more narrowly claims "a heterologous reporter nucleic acid, wherein said expression system is integrated into a nucleic acid in a manner such that it is known to be inactive under wild-type conditions but not positionally silenced" which is



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encompassed by the instant application's broader claim to "a coding sequence operable linked to a TERT promoter, under conditions such that in absence of said small molecule, transcription of said coding sequence is repressed in a cell". Also, although the copending application does not specifically described "GC-Box5 repressor binding site repression", it more broadly claims modulating "transcription control activity of a TERT promoter". In the instant case, modulating CG-Box 5 repressor binding site activity by a multitude of ways is an example of "transcription control activity of a TERT promoter", and therefore is encompassed by the copending claimed invention. More narrowing claims of the copending application are drawn to enhancing transcription controlled by the TERM promoter nucleic acid, which is also present in the instant application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 46, 48, and 49 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in

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the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue".

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

At the time of filing, GC-Box elements, their general function, and the hTERT promoter were well characterized in the art. Factors that regulating TERT promoter expression were being elucidate and the role GC-Box elements had in TERT promoter activity were being established as well. For example, repressors of human TERT promoter activity by Wilm's Tumor 1 tumor suppressor (Oh et al. J Biol Chem 274(52):

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37473-37478, 1999, see abstract) and Mad (Oh et al. *Oncogene* 19:1485-1490, 2000; see abstract) had been established, as well as an E-box and three GC-box elements, that bind c-Myc, Sp1 and Sp3, respectively, had been identified as promoters of mouse TERT activity (Nozawa et al. *J Biol Chem* 276(25):22016-22023, 2001; p.22018, col 2, par 3, lines 4-6).

The examples from the instant application demonstrate that deletion of -94 to -70, which corresponds to GC-Box 5, results in increased activity of applicant's hTERT promoter in MRC5 cells, which indicates a repressor function of GC-Box 5 in MRC5 cells (p. 35, lines 5-7 and p.36, line 1 and 2). Similarly in postfiling art, Horikawa et al (*PNAS* 102(51):18347-18442, 2005, p. 18440, col 2 par 2) describe a similar repression of hTERT promoter activity in fibroblasts with the same GC-Box core nucleic acids as CG-Box of the instant invention.

However, the instant invention lays claims to a method comprising: (a) contacting an agent, more specifically a small molecule, with an expression system comprising a GC-Box 5 repressor binding site and a coding sequence operably linked to a TERT promoter, under conditions such that in absence of said small molecule, transcription of said coding sequence is repressed in a cell; (b) determining whether transcription of said coding sequence is repressed in the presence of said small molecule; and (c) identifying said small molecule as an agent that inhibits GC-Box repression of TERT transcription if transcription of said coding sequence is not repressed in the presence of said small molecule.

While demonstrating that the GC-Box 5 sequence is present in their hTERT promoter expression system that when modified or deleted results in increased hTERT transcriptional activity in MRC5 cells, the applicant has not provided enough information describing the manner by which the repressive element functions to encompass the broad nature of the claimed invention and therefore to enable the instant invention.

The artisan would need more guidance describing how the repressive element functions and how an agent or small molecule would be involved in the repressive function. Without this type of information, the level of experimentation and discovery on the part of the artisan would be undue.

For example, the claimed invention calls for contacting an agent or small molecule with an expression system containing a GC-Box 5 and TERT promoter in a cell. Artisan would have to determine if an agent or small molecule needs to contact the GC-Box 5 directly or perhaps maybe indirectly via blocking a cofactor that need to bind the GC-Box 5. An artisan would also have to determine how to "contact an expression system" in a cell. Treating cells with an agent or small molecule that then coincides with increased TERT transcriptional activity does not necessarily mean that the inhibition of repression has occurred via the GC-Box5 element. Another repressor element may be function solely or in conjunction with GC-Box 5. Other repressor elements, such as WNT1 and Mad, have been disclosed as having repressive function in the hTERT promoter (Oh et al. J Biol Chem 274(52): 37473-37478, 1999, see abstract; Oh et al. Oncogene 19:1485-1490, 2000; see abstract).

Artisan would also have to determine if the GC-Box 5 is present and functioning in their TERT promoter as claimed in the invention. Horikawa et al. demonstrate that the analogous repressive GC-Box element in their hTERT system is not present in the mouse TERT promoter (p18440, col 2, par 2, lines 12-16), suggesting that various TERT promoters are regulated by different mechanism. Furthermore, Horikawa et al demonstrated that if the analogous GC-Box element is moved upstream, it no longer functions as a repressor element suggesting a positional requirement as well (p. 18440, col 2, par 2, lines 39-42). Also an artisan would have to determine if the instant invention could be utilized in any cell as claimed in the invention or would need a specific cellular environment with specific factors to function properly as a repressor element to TERT activity. The instant specification only demonstrates that the GC-Box 5 functions as a repressor element in MRC5 cells (example 1, p. 36, lines 1-2). Given little is known about how the GC-Box 5 functions in the instant invention, it is possible that other cofactors and transcription factors are needed. Furthermore, the GC-Box 5 element may be functioning in a more complex manner than disclosed by the claimed invention. Horikawa et al. also discloses the their analogous repressive GC-Box also overlaps with another GC-Box element that binds Sp1/Sp3 complex (p. 18439, Figure 2a), therefore suggesting involvement of the Sp1/Sp3 complex in repression their hTERT promoter activity in conjunction to the repressive GC-Box element.

All these factor would need to be addressed by an artisan to make or use the instant invention. Given the amount of empirical experimentation necessary to address and more definitively define the meets and bounds in the use the of instant invention, an

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artisan would not be enabled to make or use the instant invention without undue experimentation.

### ***Relevant Art***

7. Nozawa et al. J Biol Chem 276(25):22016-22023, 2001 demonstrates that Sp1 and Sp3, factors known to function through binding of GC-boxes, modulate the transcriptional activity of the mouse TERT promoter in C2C12 myoblasts. C2C12 myoblasts were cotransfected with one of the expression vectors for Sp1 or Sp3 together with a reporter plasmid containing mouse TERT core promoter. Sp1 and Sp3 induced a large transactivation of the TERT promoter activity (p. 22020, col 1, lines 1-8). Nozawa et al also teaches that Sp3 is considered to be bifunctional such that it represses Sp1 mediated activity of several promoters.

Nozawa et al was considered for a potential 103a rejection because it demonstrated that GC-Box elements are present in TERT promoters and function as regulators of TERT activity and that the Sp3 has inhibitory properties in some GC-Box systems, therefore it would have been obvious that the GC-Box 5 would modulate TERT transcriptional activity. Given the fact that little is known about the GC-Box 5 in the instant application and what possible mechanisms are involved in GC-Box and the fact that the GC-box regulation in Nozawa was promoting TERT promotional activity directly, the 103 rejection was not given.

8. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcia S. Noble whose telephone number is (571) 272-5545. The examiner can normally be reached on M-F 9 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Marcia S. Noble

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